

PCT

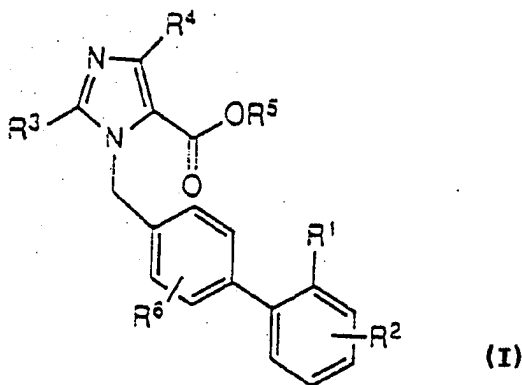
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>5</sup> : C07D 233/90, 403/10 A61K 31/415</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 94/03435</b>  (43) International Publication Date: 17 February 1994 (17.02.94)</p>
<p>(21) International Application Number: PCT/US93/07103 (22) International Filing Date: 2 August 1993 (02.08.93)  (30) Priority data: 07/926,795                      6 August 1992 (06.08.92)                      US  (71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).  (72) Inventors: ARDECKY, Robert, John ; 607 Chambers Rock Road, Landenberg, PA 19350 (US). ENSINGER, Carol, Lee ; 19 Mary Ella Drive, Newark, DE 19711 (US). PRUITT, James, Russell ; 38A Skycrest Drive, Landenberg, PA 19350 (US).</p>		<p>(74) Agents: CHRISTENBURY, Lynne, M. et al.; E.I. du Pont de Nemours and Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).  (81) Designated States: AU, BR, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i></p>

(54) Title: PRODRUGS OF IMIDAZOLE CARBOXYLIC ACIDS AS ANGIOTENSIN II RECEPTOR ANTAGONISTS



(57) Abstract

Prodrugs of imidazole carboxylic acids of formula I which are AII antagonists useful in treating hypertension, pharmaceutical compositions thereof and a method of treating hypertension using such prodrugs are disclosed.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

Title

5 Prodrugs of Imidazole Carboxylic Acids as  
Angiotensin II Receptor Antagonists

Field of the Invention

This invention relates to substituted imidazoles useful as angiotensin II (AII) blockers, and more  
10 particularly, to prodrugs of imidazole carboxylic acids which are AII antagonists useful in treating hypertension or congestive heart failure.

Background of the Invention

15 Compounds which inhibit the action of the hormone angiotensin II (AII) and are useful in alleviating angiotensin induced hypertension constitute the subject matter of a tremendous amount of research.

PCT Application, International Publication Number  
20 WO 92/00977 published January 23, 1992, discloses 4-alkylimidazole derivatives useful as angiotensin II antagonist antihypertensive agents.

Carini and Duncia, European Patent Application Publication Number (EPA) 0 253 310, published  
25 January 20, 1988, discloses a class of imidazole angiotensin II antagonists useful for treatment of hypertension and congestive heart failure. The compounds are active when administered by intravenous injection. Several of the compounds are also orally  
30 active. The general disclosure encompasses certain 4-alkyl-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]imidazoles substituted at the 5-position of the imidazole ring with halogen, nitro, trifluoromethyl or cyano.

Carini, Duncia and Wong, International Application Publication Number WO 89/06233, published July 13, 1989, discloses the same class of imidazole angiotensin II antagonists and also discloses additional imidazole  
5 angiotensin II antagonists useful for treatment of hypertension and congestive heart failure. Some of the additionally-disclosed compounds are orally active. The general disclosure of WO 89/06233 encompasses the compounds of this invention, but the compounds of this  
10 invention are not specifically disclosed.

PCT Application, International Publication Number WO 91/00277 published January 10, 1991, discloses substitutes imidazoles useful as AII blockers. The compounds describes have activity in treating  
15 hypertension and congestive heart failure.

PCT Application, International Publication Number WO 91/00281 published January 10, 1991, describes fused-ring aryl substituted imidazoles useful as AII blockers. The compounds described have activity in treating  
20 hypertension and congestive heart failure.

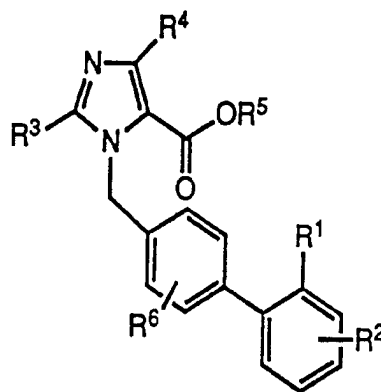
European Patent Application Publication Number 0 434 249 A2 published June 26, 1991 describes benzofuran derivatives useful in treatment or prophylaxis of hypertension and potentially useful for  
25 the treatment of cognitive disorders and other diseases such as renal failure, hyperaldosteronism, cardiac insufficiency, congestive heart failure, post-myocardial infarction, cerebrovascular disorders, glaucoma and disorders of intracellular homeostasis.

30 European Patent Application Publication Number 0 459 136 A1 published April 12, 1991 describes benzimidazole derivatives having AII antagonistic activity and antihypertensive activity.

Compounds which inhibit AII such as imidazole  
 carboxylic acid AII blockers can have poor absorption in  
 the gastrointestinal tract. One way in which  
 bioavailability of such compounds might be improved  
 5 would involve designing a prodrug which would hydrolyze  
 to the corresponding acid under physiological conditions  
 whereby this hydrolysis would occur at some point after  
 the prodrug has been absorbed in the gut thus liberating  
 the parent compound without impairing its  
 10 pharmacological activity.

#### Summary of the Invention

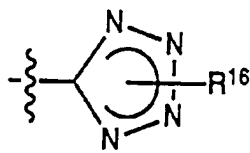
In one embodiment this invention relates to a class  
 of novel 5-imidazole carboxylic esters as represented by  
 15 Formula I:



(I)

wherein

R<sup>1</sup> is -CO<sub>2</sub>H or



20

R<sup>2</sup> is

- (a) H,
- (b) C1-C5-alkyl,
- (c) C1-C5-alkoxy,

(d) halo (F, Cl),

(e) phenyl;

$R^3$  is C1-C5-alkyl, C2-C5-alkenyl, C2-C5-alkynyl;

5  $R^4$  is

(a) H,

(b) halo (Cl, Br, I),

(c) C1-C6-alkyl,

(d)  $C_vF_w$  where  $v=1$  to 3 and  $w=1$  to  $(2v+1)$ ;

10  $R^5$  is

(a) C1-C5-alkyl,

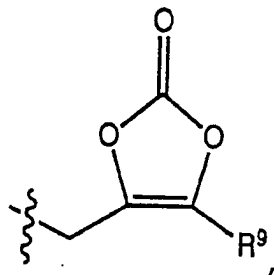
(b) C2-C5-alkenyl,

(c) C2-C5-alkynyl,

(d)  $-(CH_2)_pNR^{12}R^{13}$ ,

15 (e)  $-(CH_2)_sCH(R^7)(CH_2)_{s'}O_2CR^8$ ,

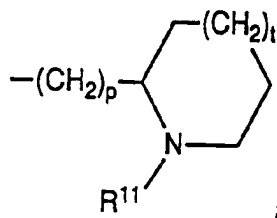
(f)



(g)  $-(CH_2)_pCO_2R^{10}$ ,

20

(h)



$R^6$  is

(a) H,

(b) halogen (F, Cl, Br, I),

25

(c) C1-C5-alkyl,

- (d) -OH,  
(e) C1-C4-alkoxy,  
(f) -NO<sub>2</sub>,  
(g) -NR<sup>12</sup>R<sup>13</sup>,  
5 (h) -NR<sup>12</sup>COR<sup>15</sup>,  
(i) -NR<sup>12</sup>CO<sub>2</sub>R<sup>15</sup>,  
(j) -S(O)<sub>r</sub>R<sup>14</sup> where r is 0, 1 or 2,  
(h) -CO<sub>2</sub>R<sup>15</sup>,  
(i) -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),  
10 (J) -OC<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1), or  
(K) -CN;

R<sup>7</sup> is H or C1-C4-alkyl;

R<sup>8</sup> is

- (a) H,  
15 (b) C1-C5-alkyl,  
(c) C1-C5-alkyl optionally substituted with a  
group consisting of:  
i) C1-C5-alkoxy,  
ii) aryl, wherein aryl is phenyl or  
20 naphthyl optionally substituted with one  
or two substituents selected from the  
group consisting of halo (F, Cl, Br, I),  
C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>,  
-S(O)<sub>r</sub>(C1-C5-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>,  
25 -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1  
to (2v+1);

R<sup>9</sup> is

- (a) C1-C5-alkyl,  
(b) -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),  
30 (c) C1-C5-alkyl optionally substituted with a  
group consisting of:  
i) C1-C5-alkoxy,  
ii) phenyl or phenyl substituted with at  
least one substituent selected from the group

consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup><sub>R13</sub>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),

5           iii) benzyl or benzyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup><sub>R13</sub>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where  
10           v=1 to 3 and w=1 to (2v+1);

R<sup>10</sup> is

(a) phenyl or phenyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup><sub>R13</sub>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where  
15           v=1 to 3 and w=1 to (2v+1),

(b) benzyl or benzyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup><sub>R13</sub>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub>  
20           where v=1 to 3 and w=1 to (2v+1);

R<sup>11</sup> is H, C1-C5-alkyl or benzyl;

25   R<sup>12</sup> and R<sup>13</sup> are independently H, C1-C5-alkyl, phenyl or benzyl;

R<sup>14</sup> is CF<sub>3</sub>, C1-C5-alkyl, or phenyl;

R<sup>15</sup> is H, C1-C5-alkyl, or NR<sup>12</sup><sub>R13</sub>;

R<sup>16</sup> is H or CH<sub>2</sub>O<sub>2</sub>CC(CH<sub>3</sub>)<sub>3</sub>;

30   p is 1-5;

r is 0-2;

s and s' are 0-5;

t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In a second embodiment, this invention relates to pharmaceutical compositions comprising a pharmaceutically suitable carrier and a therapeutically effective amount of the compounds of this invention.

5 In a third embodiment, this invention concerns a method of treating hypertension in a warm-blooded animal comprising orally administering to the animal a therapeutically effective amount of a compound of the invention.

10 In a fourth embodiment, this invention concerns a method of treating congestive heart failure in a warm-blooded animal comprising orally administering to the animal a therapeutically effective amount of a compound of the invention.

15

#### Detailed Description of the Invention

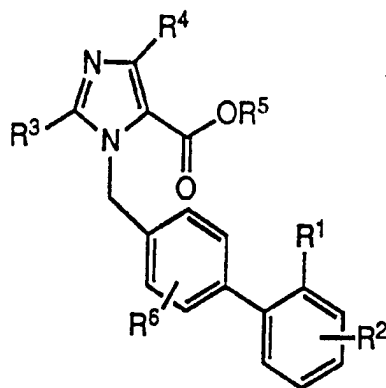
The compounds of this invention exhibit remarkable and unexpected potency as antihypertensive agents in comparison to the compounds specifically disclosed in  
20 EPA 0 253 310 and WO 89/06233 which have been tested.

More specifically, the compounds of the invention which have been tested all have equal or greater oral antihypertensive potency than any of the compounds specifically disclosed in EPA 0 253 310 and WO 89/06233  
25 which have been tested.

The compounds of the invention are also highly active antihypertensive agents when administered by intravenous injection.

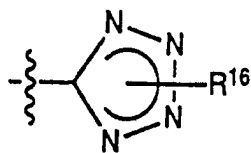
The compounds of the invention are 5-imidazole  
30 carboxylic ester having the general Formula I:

8



I

wherein

R<sup>1</sup> is -CO<sub>2</sub>H orR<sup>2</sup> is

- (a) H,  
 (b) C1-C5-alkyl,  
 (c) C1-C5-alkoxy,  
 (d) halo (F, Cl),  
 (e) phenyl;

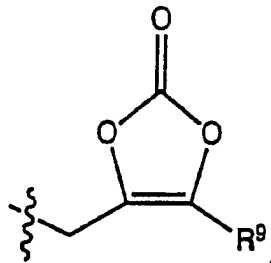
R<sup>3</sup> is C1-C5-alkyl, C2-C5-alkenyl, C2-C5-alkynyl;R<sup>4</sup> is

- (a) H,  
 (b) halo (Cl, Br, I),  
 (c) C1-C6-alkyl,  
 (d) C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1);

R<sup>5</sup> is

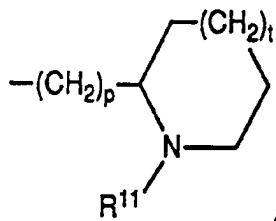
- (a) C1-C5-alkyl,  
 (b) C2-C5-alkenyl,  
 (c) C2-C5-alkynyl,  
 (d) -(CH<sub>2</sub>)<sub>p</sub>NR<sup>12</sup>R<sup>13</sup>,  
 (e) -(CH<sub>2</sub>)<sub>s</sub>CH(R<sup>7</sup>)(CH<sub>2</sub>)<sub>s'</sub>O<sub>2</sub>CR<sup>8</sup>,

(f)

(g)  $-(CH_2)_pCO_2R^{10},$ 

5

(h)

 $R^6$  is

- (a) H,  
 (b) halogen (F, Cl, Br, I),  
 10 (c) C1-C5-alkyl,  
 (d) -OH,  
 (e) C1-C4-alkoxy,  
 (f) -NO<sub>2</sub>,  
 (g) -NR<sup>12</sup>R<sup>13</sup>,  
 15 (h) -NR<sup>12</sup>COR<sup>15</sup>,  
 (i) -NR<sup>12</sup>CO<sub>2</sub>R<sup>15</sup>,  
 (j) -S(O)<sub>r</sub>R<sup>14</sup> where r is 0, 1 or 2,  
 (h) -CO<sub>2</sub>R<sup>15</sup>,  
 (i) -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),  
 20 (J) -OC<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1), or  
 (K) -CN;

 $R^7$  is H or C1-C4-alkyl; $R^8$  is

- (a) H,  
 25 (b) C1-C5-alkyl,

(c) C1-C5-alkyl optionally substituted with a group consisting of:

- 5           i) C1-C5-alkoxy,  
          ii) aryl, wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C5-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>,  
10           -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1);

R<sup>9</sup> is

- (a) C1-C5-alkyl,  
          (b) -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),  
15          (c) C1-C5-alkyl optionally substituted with a group consisting of:

- i) C1-C5-alkoxy,  
          ii) phenyl or phenyl substituted with at least one substituent selected from the group  
20          consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),

- iii) benzyl or benzyl substituted with  
25          at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1);

30   R<sup>10</sup> is

- (a) phenyl or phenyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-

alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where  
v=1 to 3 and w=1 to (2v+1),

- (b) benzyl or benzyl substituted with at  
least one substituent selected from the group  
5 consisting of halo (F, Cl, Br, I), C1-C4-  
alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-  
alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub>  
where v=1 to 3 and w=1 to (2v+1);

R<sup>11</sup> is H, C1-C5-alkyl or benzyl;

- 10 R<sup>12</sup> and R<sup>13</sup> are independently H, C1-C5-alkyl,  
phenyl or benzyl;

R<sup>14</sup> is CF<sub>3</sub>, C1-C5-alkyl, or phenyl;

R<sup>15</sup> is H, C1-C5-alkyl, or NR<sup>12</sup>R<sup>13</sup>;

R<sup>16</sup> is H or CH<sub>2</sub>O<sub>2</sub>CC(CH<sub>3</sub>)<sub>3</sub>;

- 15 p is 1-5;

r is 0-2;

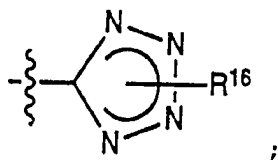
s and s' are 0-5;

t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

- 20 Preferred for their antihypertensive activity are  
novel compounds of Formula I above wherein

R<sup>1</sup> is



R<sup>2</sup> is H;

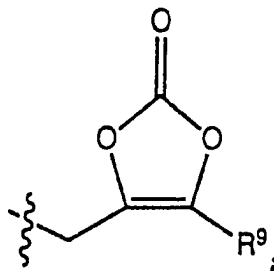
- 25 R<sup>3</sup> is C1-C5-alkyl;

R<sup>5</sup> is

(a) -(CH<sub>2</sub>)<sub>s</sub>CH(R<sup>7</sup>)(CH<sub>2</sub>)<sub>s'</sub>O<sub>2</sub>CR<sup>8</sup>,

12

(b)



R<sup>6</sup> is H;

R<sup>7</sup> is H;

5 R<sup>8</sup> is

(a) H,

(b) C1-C5-alkyl,

(c) C1-C5-alkoxy,

(c) C1-C5-alkyl optionally substituted with a  
10 group consisting of:

i) C1-C5-alkoxy;

R<sup>9</sup> is

(a) C1-C5-alkyl;

(b) C1-C5-alkyl optionally substituted with a  
15 group consisting of:

i) C1-C5-alkoxy,

ii) phenyl or phenyl substituted with at  
least one substituent selected from the group  
consisting of halo (F, Cl, Br, I), alkyl, C1-  
20 C5-alkoxy, -OH,

iii) benzyl or benzyl substituted with at  
least one substituent selected from the group  
consisting of halo (F, Cl, Br, I), C1-C5-  
alkoxy, -OH;

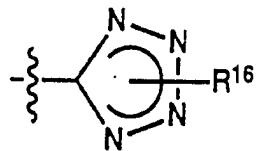
25 p is 1;

s is 1;

s' is 0.

Most preferred are compounds having the Formula I  
above wherein

R<sup>1</sup> is



R<sup>2</sup> is H;

R<sup>3</sup> is C1-C5-alkyl;

5 R<sup>5</sup> is  $-(CH_2)_sCH(R^7)(CH_2)_{s'}O_2CR^8$ ;

R<sup>7</sup> is H;

R<sup>8</sup> is

(a) C1-C5-alkoxy,

(b) C1-C5-alkyl,

10 (c) C1-C5-alkyl optionally substituted with a group consisting of:

i) C1-C5-alkoxy;

p is 1;

s is 1.

15 Specifically preferred are the following:

- Trimethylacetoxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate;
- Methoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate;
- 20 • t-Butoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate;
- 25 • 1-(Methoxycarbonyl)ethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate.

This invention also relates to pharmaceutical compositions containing these novel imidazole carboxylic acids and pharmaceutical methods using them.

30

Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in Remington's Pharmaceutical Science, 17th Edition, page 1418 (1985). It is well known to one  
5 skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts.

10 Also within the scope of this invention are pharmaceutical compositions comprising a suitable pharmaceutical carrier and a compound of Formula I to treat hypertension or congestive heart failure.

The disclosure of all publications and references  
15 mentioned herein are hereby incorporated by reference unless indicated otherwise.

### Synthesis

The compounds of Formula I can be prepared using  
20 the reagents and materials described herein. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected.

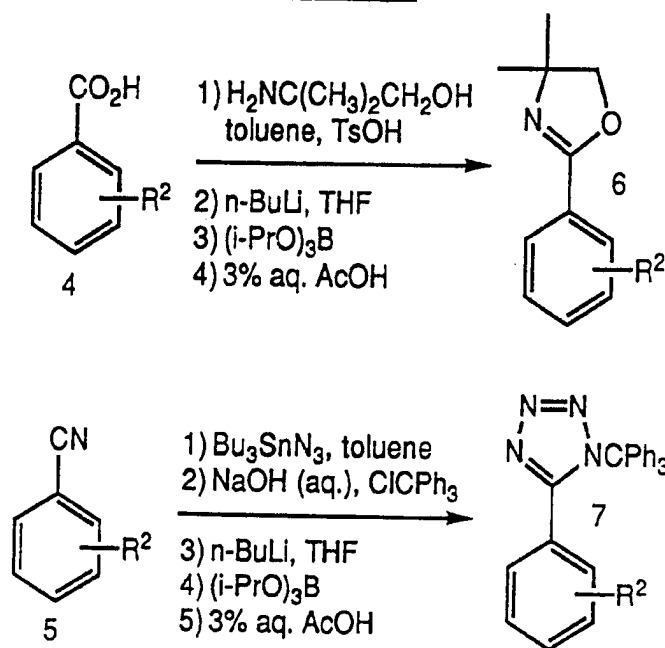
Synthesis of the terminal, substituted phenyl ring  
25 of the biphenyl region of compounds having the structure of Formula I above is described in Scheme 1. Carboxylic acids (4), which are commercially available, can be protected with 2-amino-2-methylpropanol to form oxazolines (5) using the procedure described in *J. Am.*  
30 *Chem. Soc.* 97: 7383 (1975). Ortho lithiation of the oxazoline with butyl lithium followed by quenching with triisopropyl borate and borate hydrolysis with aqueous acetic acid gives phenyl boronic acid (6) as is

described in U. S. Patent No. 5,130,439 issued July 14, 1992.

Similarly, nitriles (5) which are also commercially available can be treated with tributyl tin chloride and sodium azide to prepare the corresponding tin tetrazole which is used in situ. Tributyl tin is removed using sodium hydroxide and the resulting tetrazole is protected with trityl chloride. As discussed above, the corresponding tetrazolyl phenyl boronic acids (7) are produced using ortho lithiation with butyl lithium, quenching with triisopropyl borate and hydrolysis with aqueous acetic acid as is described in U.S. Patent No. 5,130,439 issued July 14, 1992.

15

Scheme 1

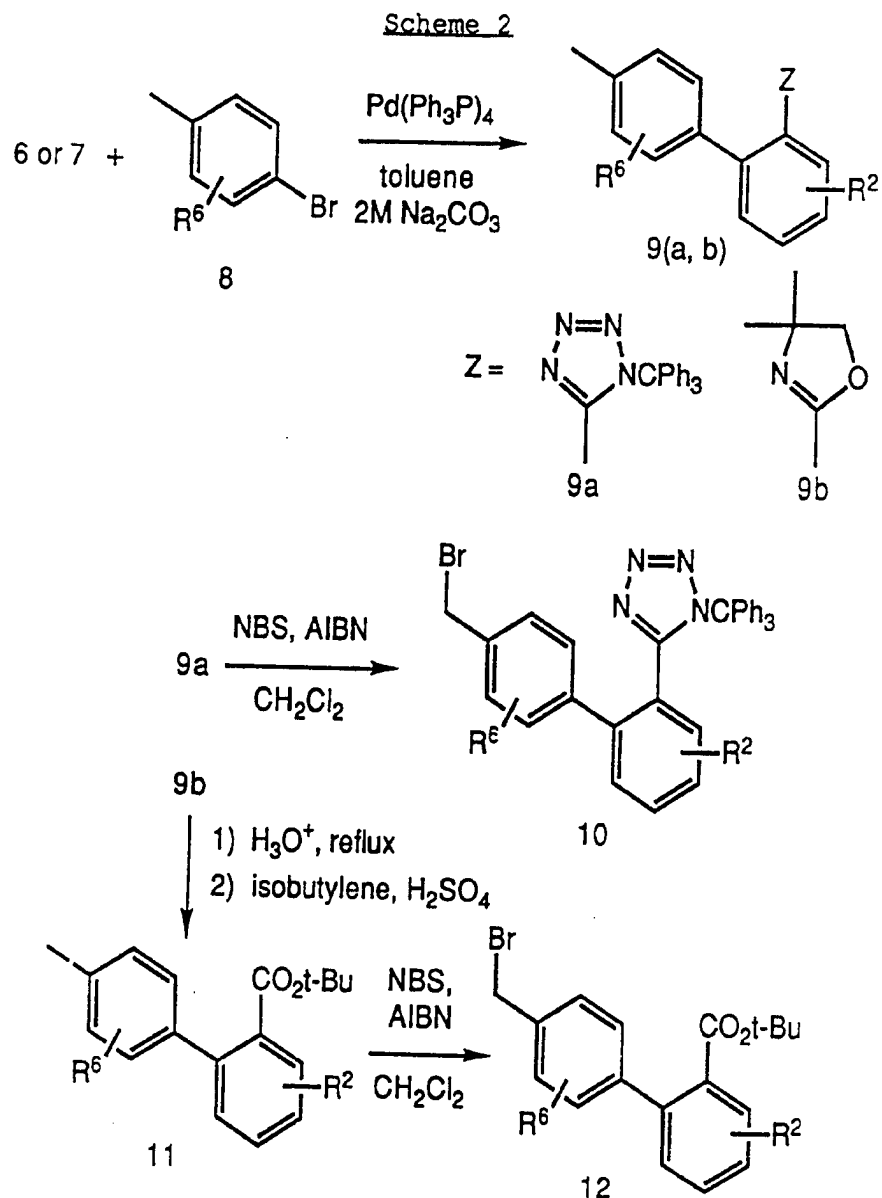


Biphenyl compounds (10) or (12) can be prepared using the procedure illustrated in Scheme 2 below.

Boronic acids (6) or (7) are coupled to halides (8) using tetrakis(triphenylphosphine) palladium catalyst in

toluene and 2M sodium carbonate to produce biphenyl compounds (9(a,b)) as described in *Syn. Comm.*, 11: 513 (1981). Bromination of biphenyl compounds (9a) with N-bromosuccinimide (NBS) using azobisisobutyronitrile (AIBN) as a catalytic initiator according to the procedure described in U.S. Patent No. 4,820,843 issued April 11, 1989 produces the corresponding bromide compounds (10). Alternatively, compound (9b) can be hydrolyzed with aqueous mineral acid then reprotected with isobutylene and a catalytic amount of sulfuric acid to produce t-butyl esters (11) which can be brominated using NBS to produce the corresponding bromides (12).

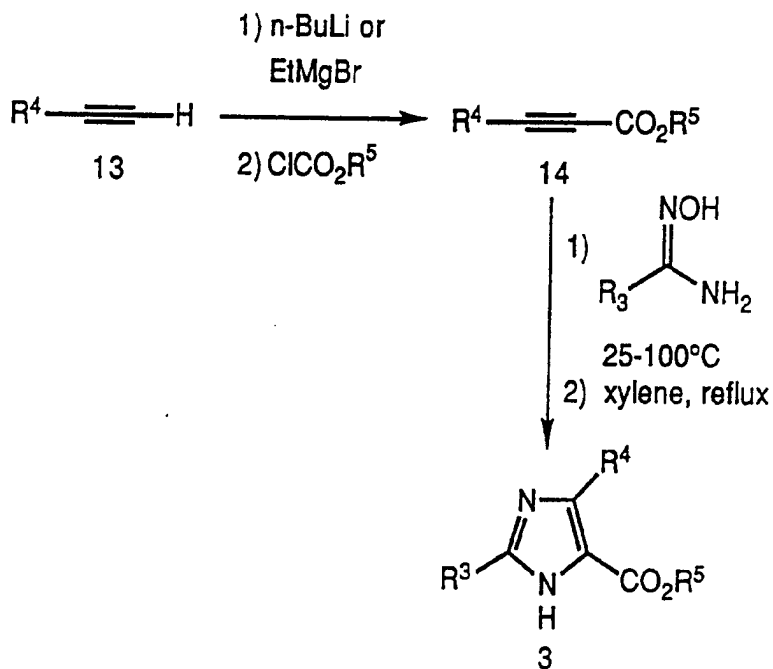
17



Synthesis of the imidazole portion of the compounds  
 5 of Formula I are described in Scheme 3. Commercially  
 available terminal acetylenes (13) are deprotonated with  
 either n-butyl lithium or ethyl magnesium bromide and  
 quenched with the appropriated chloroformate to produce  
 esters (14). Imidazoles (3) are made by reacting these  
 10 esters (14) with amidoximes, prepared according to the

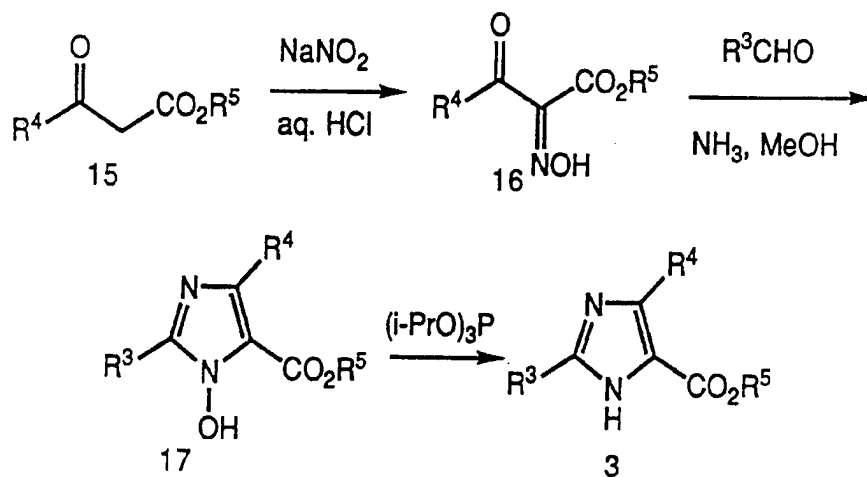
procedure described in Cancer Research 38: 1291 (1978), followed by addition of xylene and refluxing for several hours.

5

Scheme 3

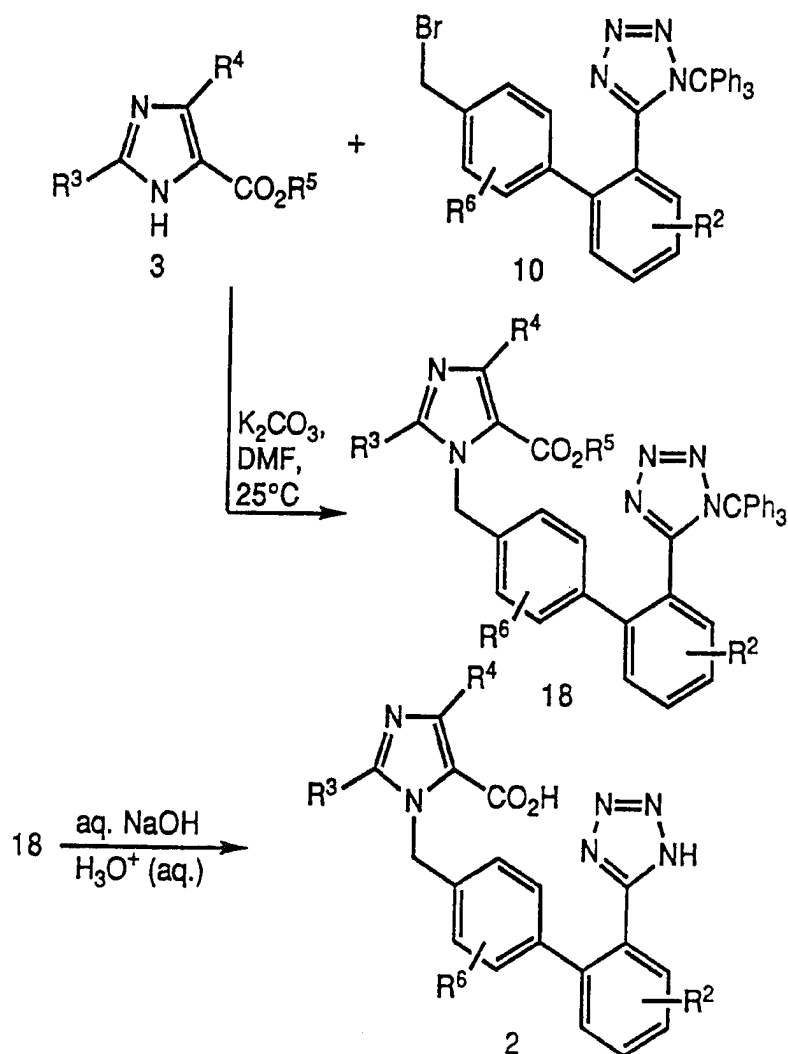
An alternative approach is set forth in Scheme 4. This alternative approach is desirable if a larger quantities of the imidazole (3) are needed. Commercially available  $\beta$ -ketoesters are treated with sodium nitrite in aqueous hydrochloric acid to make oximes (16). Condensation with ammonia in methanol provides N-hydroxyimidazoles (17). Deoxygenation of the n-hydroxyimidazoles (17) with triisopropylphosphite produces the corresponding imidazoles (3).

Scheme 4



5 Preparation of compounds of Formula I wherein  $R^5$  is H are set forth in Scheme 5. Imidazoles (3) are alkylated with bromomethylbiphenyl compounds (10) using potassium carbonate in dimethylformamide (DMF) as described in PCT Patent Application having International  
 10 Publication Number WO 92/009777 published January 23, 1992. These alkylations produce a mixture of regioisomers in which the major product is the regioisomer corresponding to compound (18). Carboxylic acids (2) are obtained by removing the trityl protecting  
 15 groups using aqueous sodium hydroxide followed by an aqueous acid such as 1 N hydrochloric acid.

Scheme 5

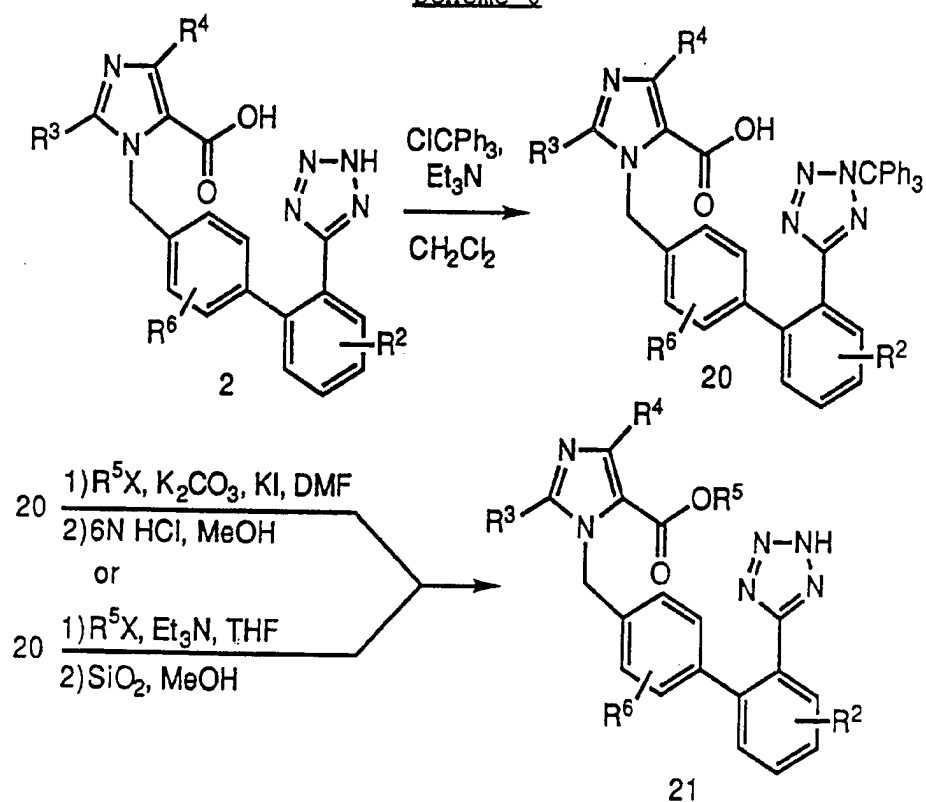


5 Alkylation of carboxylic acids (2) is described in Scheme 6 below. The tetrazole compounds (2) is  
 10 protected with a trityl group by treating with trityl chloride in the presence of triethylamine to produce the corresponding tetrazoles (20) which are then alkylated  
 with the appropriate alkyl halide using a catalytic amount of potassium iodide in the presence of potassium carbonate. The tetrazole is deprotected by treating

with hydrochloric acid in methanol to produce tetrazoles (21).

An alternative approach involves alkylating compounds (20) with the appropriate alkyl halide and triethylamine in tetrahydrofuran (THF). Deprotection with silica gel in methanol produces tetrazoles (21).

Scheme 6

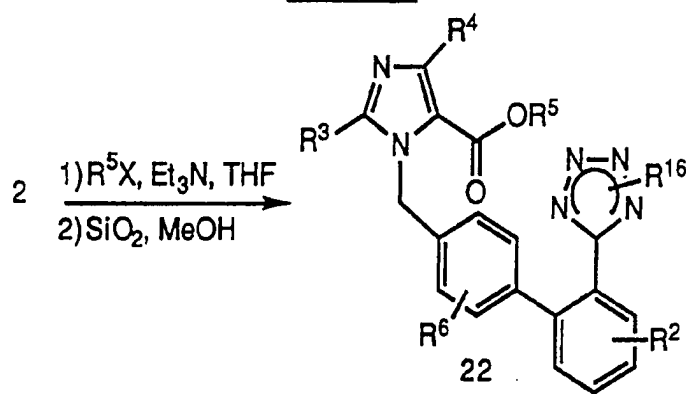


10

If the trityl protecting group is not used then alkylation of compounds (2) with the appropriate alkyl halide occurs at both the carboxylic acid and the tetrazole as shown in Scheme 7 to produce compounds (22).

15

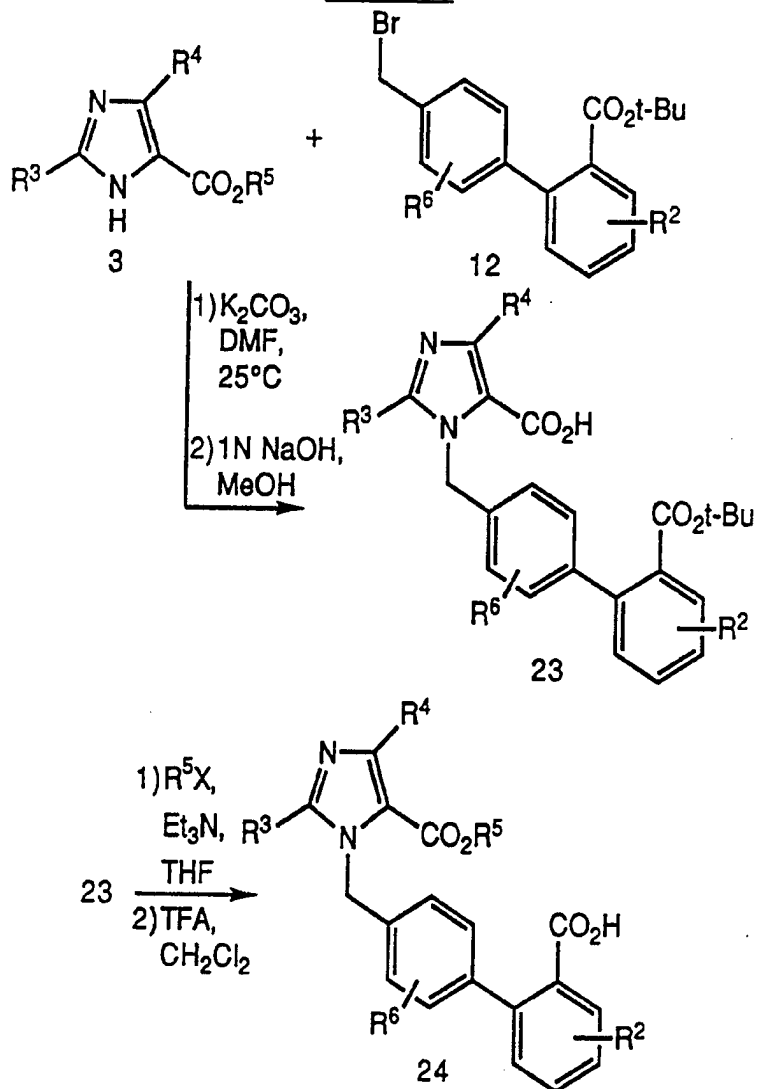
Scheme 7



Alkylation of imidazoles (3) with bromides (12)  
 5 followed by monohydrolysis with 1 N sodium hydroxide in  
 methanol produces esters (23) which can then be  
 alkylated with the appropriate alkyl halide in  
 triethylamine and THF. Deprotection with  
 trifluoroacetic acid (TFA) in methylene chloride  
 10 produces the acids (24).

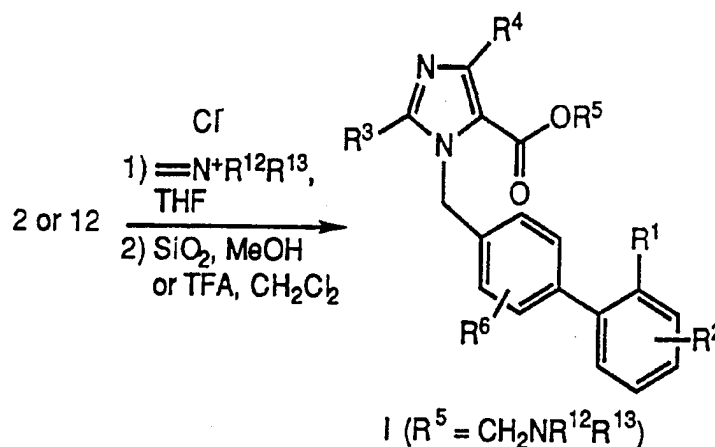
23

Scheme 8



Preparation of compounds of Formula I where  $R^5$  is  $CH_2NR^{12}R^{13}$  can be prepared as outlined in Scheme 9 below. The appropriate imonium salt is added to the carboxylic acid (2) or (12) to form the corresponding amine which can then be deprotected to give the desired compounds.

Scheme 9



Preparation of the appropriate alkyl halides can  
 5 found in Curran and Ross, U.S. Patent 4,914,091, issued  
 April 3, 1990, *Journal of Antibiotics* 40, 370-84, 1987,  
 and *Chemical and Pharmaceutical Bulletin* 32, 2241,  
 (1984).

The compounds of this invention and their  
 10 preparation can be understood further by the following  
 examples, which do not constitute a limit of the  
 invention. In these examples, unless otherwise  
 indicated, all temperatures are in degrees centigrade  
 and parts and percentages are by weight. The  
 15 disclosures of all references cited herein are hereby  
 incorporated by reference unless otherwise indicated.

#### Example 1

##### Preparation of

20 Propyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-  
 4-yl]methyl]imidazole-5-carboxylate

##### PART A: Preparation of Butyramidoxime

347.5 g of hydroxylamine hydrochloride was  
 25 dissolved in 3500 mL methanol and cooled to 0°C. A 50%

aqueous solution of sodium hydroxide (412 g NaOH) was slowly added and allowed to stir at room temperature for 30 minutes. The precipitate was filtered and 435 mL of butyronitrile was added to the filtrate. The mixture  
5 was stirred for an additional 16 hours and 500 mL water was added. The reaction was evaporated to remove the methanol, extracted with ethyl acetate, the organic extracts dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated to give 306 g product.  
10 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.96 (t, 3H), 1.59 (t, 2H), 2.12 (t, 2H), 4.56 (bs, 2H).

PART B: Preparation of Methyl 4-ethyl-2-propylimidazole-5-carboxylate

15 93 g of methyl pentynoate and 82 g butyramidoxime are mixed together without solvent and heated to 50°C for 24 hours. 400 mL xylene was added and water was azeotropically removed for 6 hours. The reaction was then distilled (140°C at 0.2 torr) to give 44 g product.  
20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.99 (t, 3H), 1.15 (t, 3H), 1.65 (m, 2H), 2.71 (m, 2H), 2.97 (q, 2H), 3.87 (s, 3H).

PART C: Preparation of 2-(2'-Triphenylmethyl-2'H-tetrazol-5'-yl)phenylboronic acid

25 To a 22 L flask under nitrogen purge was charged 8.25 L acetone, followed by 1.1 kg 5-phenyltetrazole. Triethylamine (800 g) was added in such a rate that the temperature was maintained below 35°C with some cooling. Solid trityl chloride was charged to this suspension in  
30 five 440 g portions. The temperature was maintained below 35°C. An additional 1.38 L acetone was added to the reaction which was then maintained at 25° to 30°C with stirring for 2 hours. Water (2.2 L) was added and the mixture was chilled to 15° to 20°C. The solid was

collected by filtration; the filter cake was rinsed with 1.65 L 50% acetone-water followed by excess amount of water. The wet cake was re-slurried in 8 L acetone and 8 L of water was added slowly. The suspension was  
5 stirred for 1 hour then filtered. The filter cake was rinsed with 3 to 5 L of water. The white solid was dried in a vacuum oven at 40°-45°C to a constant weight of 3.0 kg, mp 158-160°C.

To a dry 12 L flask under nitrogen purge was  
10 charged 3.19 L of dry tetrahydrofuran. With agitation, 398 g of 5-phenyl-1-trityl-tetrazole prepared above was charged. The system was evacuated and released to nitrogen three times and then cooled to -20°C. A solution of n-butyl lithium in heptane (1.6 M, 477 g)  
15 was then added to the reaction mixture while maintaining the temperature at -15°C to -20°C. The resultant deep red solution was stirred at -5°C for 1 hour during which time the lithium salt crystallized out. The solid suspension was cooled to -25°C again and 333 g  
20 triisopropylborate was charged at a temperature range of -20°C to -25°C. After the addition, the mixture was allowed to warm to 20°C without heating. About 2.5 L of solvent was removed by vacuum distillation while the pot temperature was kept below 40°C. To the mixture was  
25 then added 2.66 L of 3% acetic acid and the resultant suspension was stirred for 1 hour. The white solid was collected by filtration. The solid cake was rinsed with 1.5 L of 20% tetrahydrofuran in water, followed by 3 L of water. The solid was dried under vacuum at room  
30 temperature to a constant weight of 502.3 g, mp 142-146°C (dec.).

PART D: Preparation of 2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methane

1.02 g of 4-bromotoluene, 2.16 g of phenyl boronic acid, 1.38 g potassium carbonate, 0.15 g tetrabutyl ammonium bromide and 1 mL water are mixed together. 0.18 g of tetrakis(triphenylphosphine) palladium is added and the vacuum purged with nitrogen three times. The reaction was refluxed for 6 hours, cooled and diluted with a mixture of toluene and water. The mixture was separated and the aqueous layer was extracted with toluene, dried with  $\text{MgSO}_4$ , filtered and evaporated to give 1.87 g of crude product. This material was taken on without purification.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  2.4 (s, 3H), 6.9 (d, 6H), 7.22-7.5 (m, 16H), 7.97 (m, 1H).

PART E: Preparation of 2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methyl bromide

2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methane (52.07 g, 109 mmol, 1 eq), N-bromosuccinimide (19.4 g, 109 mmol, 1 eq), benzoyl peroxide (1.0 g) and carbon tetrachloride (300 mL) were mixed and refluxed for 2.5 hours. The reaction was cooled to room temperature and the succinimide filtered. The filtrate was concentrated and the residue triturated with ether to yield a first crop of 36.0 g of product. This material was suitable for further transformation.

mp 129.5-133.0°C (dec.).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  4.37 (s, 2H), 6.9 (d, 6H), 7.22-7.5 (m, 16H), 7.97 (m, 1H).

PART F: Preparation of Methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.053 g of methyl 4-ethyl-2-propylimidazole-5-carboxylate, 0.12 g 2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methyl bromide and 0.38 g potassium carbonate were dissolved/suspended in 10 mL DMF. The reaction was stirred overnight and then evaporated. The crude oil was chromatographed with ethyl acetate/hexanes (3:7) to give 0.14 g of the desired regioisomer.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  0.96 (t, 3H), 1.21 (t, 3H), 1.67 (m, 2H), 2.58 (t, 2H), 2.85 (q, 2H), 3.77 (s, 3H), 5.42 (s, 2H), 6.82 (d, 2H), 6.92 (d, 6H), 7.22-7.5 (m, 14H), 7.92 (m, 1H).

PART G: Preparation of 4-Ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid

0.97 g of methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate is dissolved in 2 mL methanol and added to 10 mL 3N potassium hydroxide. This was allowed to reflux for 6 hours then cooled to room temperature. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  then acidified with 1 N HCl to pH 4 to give 0.52 g of product which precipitated and was isolated by filtration.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  0.93 (t, 3H), 1.31 (t, 3H), 1.66 (m, 2H), 2.57 (t, 2H), 2.8 (q, 2H), 5.44 (s, 2H), 6.86 (d, 2H), 7.20 (d, 2H), 7.25-7.5 (m, 3H), 7.88 (m, 1H).

Part H: Preparation of 4-Ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid

A mixture of 7.5 g of 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid, 5.17 g trityl chloride and 1.92 g triethylamine in 50 mL CH<sub>2</sub>Cl<sub>2</sub> is stirred overnight. After water addition and acidification with 1N HCl to pH 3, the mixture was separated and the organic phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate (1:1). The mixture was dried with Na<sub>2</sub>SO<sub>4</sub>, suction filtered and the solvent evaporated. 6.46 g of product was obtained after flash chromatography with ethyl acetate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.93 (t, 3H), 1.22 (t, 3H), 1.62 (m, 2H), 2.51 (t, 2H), 2.92 (q, 2H), 5.4 (s, 2H), 6.76 (d, 2H), 6.91 (m, 6H), 7.04 (d, 2H), 7.2-7.35 (m, 10H), 7.43 (m, 2H), 7.89 (m, 1H).

Part I: Preparation of Propyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate

1.32 g of 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid, 0.39 mL of iodopropane and 0.55 g potassium carbonate were added to 6 mL DMF. The reaction was allowed to stir for 24 hours then diluted with 12 mL water and 90 mL ethyl acetate. The organic layer was separated and washed five times with water, once with brine and dried with MgSO<sub>4</sub>. Chromatography with a gradient from 5 to 50% ethyl acetate in hexane gave 0.96 g of desired product.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.85 (t, 3H), 0.95 (t, 3H), 1.26 (t, 3H), 1.65 (m, 4H), 2.46 (t, 2H), 2.97 (q, 2H), 4.1

(t, 2H), 5.4 (s, 2H), 6.77 (m, 2H), 6.9 (m, 6H), 7.07 (m, 2H), 7.28 (m, 9H), 7.48 (m, 2H), 7.92 (m, 1H).

Part J: Preparation of Propyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.96 g of propyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate was dissolved in 22 mL of methanol and then 4.8 g silica gel and 6 drops of 6N HCl were added. The gel was filtered away after 3 days and the resulting silica was washed with CH<sub>2</sub>Cl<sub>2</sub> and then ethyl acetate. The combined organic solutions were evaporated and the residue was chromatographed with a gradient of 0 to 5% methanol in chloroform to provide 0.25 g of the title compound.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.8-0.95 (m, 9H), 1.45-1.65 (m, 4H), 2.15 (t, 2H), 2.48 (t, 2H), 4.07 (t, 2H), 5.4 (s, 2H), 6.74 (m, 2H), 7.05 (m, 2H), 7.27 (m, 1H), 7.48 (m, 2H), 7.77 (m, 1H).

Example 2

Preparation of

(N,N-Dimethylamino)methyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid is treated with Eschenmoser's salt in THF at room temperature overnight to give the title compound.

Example 3Preparation of

Acetoxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

5

Part A: Preparation of Chloromethyl acetate

3.90 g potassium acetate was suspended in 50 mL DMF. 7 g Iodochloromethane was added and the mixture stirred for 2.5 hours. 50 mL CH<sub>2</sub>Cl<sub>2</sub> was added and the solution was washed six times with water and dried with MgSO<sub>4</sub>. Suction filtration and evaporation of the filtrate provided 3.1 g of the ester.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 2.11 (s, 3H), 5.31 (s, 2H).

15 Part B: Preparation of Acetoxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

0.37 g of 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid was dissolved in 5 mL THF and 0.5 g chloromethyl acetate and 0.5 mL triethylamine were added. The resulting solution was stirred overnight. The solvent was evaporated and the residue dissolved in methanol with 0.25 mL acetic acid and stirred 8 hours with 10 g silica gel. The mixture was evaporated and the residue on the gel was flash chromatographed with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:9) to provide 0.124 g of the title compound.

25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.94 (t, 3H), 1.23 (t, 3H), 1.63 (m, 2H), 2.09 (s, 3H), 2.53 (t, 2H), 2.95 (q, 2H), 5.42 (bs, 4H), 6.76 (d, 2H), 7.04 (d, 2H), 7.35 (m, 1H), 7.43 (m, 2H), 7.79 (m, 1H).

Example 4Preparation of

Isobutyryloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

5

Part A: Preparation of Chloromethyl isobutyrate

Several drops of 1.0 M  $\text{ZnCl}_2$  in  $\text{Et}_2\text{O}$  solution was added to a mixture of 10.48 mL of isobutyryl chloride and 3.00 g of paraformaldehyde. The reaction exothermed and the paraformaldehyde dissolved. The mixture was stirred overnight at room temperature then in a  $90^\circ\text{C}$  oil bath for 4 hours. Distillation directly out of the reaction flask provided 6.14 g of the product (bp  $137-139^\circ\text{C}$ ).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  1.12 (d, 6H), 2.54 (m, 1H), 5.64 (s, 2H).

Part B: Preparation of Isobutyryloxymethyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

20

0.2490 g KI in one portion was added to a mixture of 0.6588 g 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid, 0.2049 g chloromethyl isobutyrate, and 0.1382 g  $\text{K}_2\text{CO}_3$  in 3 mL DMF. The mixture was stirred overnight at room temperature under Ar. The reaction was then partitioned between 8 mL  $\text{H}_2\text{O}$  and 40 mL EtOAc. The organic layer was washed once with ice cold 0.1 N sodium thiosulfate, once with  $\text{H}_2\text{O}$ , once with brine and dried with  $\text{MgSO}_4$ . After suction filtration and evaporation of the filtrate, flash chromatography with 25% EtOAc/hexanes provided 0.46 g of the desired product.

30

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  0.88 (t, 3H), 1.13 (d, 6H), 1.25 (t, 3H), 1.68 (m, 2H), 2.45-2.60 (m, 3H), 1.93 (q, 2H), 5.41 (s, 2H), 5.80 (s, 2H), 6.76 (m, 2H), 6.93 (m, 6H), 7.08 (m, 2H), 7.2-7.5 (m, 12H), 7.90 (m, 1H).

5

Part C: Preparation of Isobutyryloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

To a solution of 0.46 g isobutyryloxymethyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylate in 10 mL MeOH was added 1.5 mL glacial acetic acid and the mixture stirred 2 days at room temperature. The reaction was evaporated to near dryness and the residue purified by flash chromatography using a 0% to 5% MeOH/ $\text{CHCl}_3$  gradient. There was obtained 0.250 g of the title compound.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  0.85 (2t, 6H), 1.08 (d, 6H), 1.55 (m, 2H), 2.21 (t, 2H), 2.41-2.59 (m, 3H), 5.43 (s, 2H), 5.78 (s, 2H), 6.73 (m, 2H), 7.03 (m, 2H), 7.4-7.68 (m, 3H), 7.78 (m, 1H).

Example 5

Preparation of

Trimethylacetoxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.36 g of the title compound were obtained using the procedure described in Example 4 above using 0.242 g chloromethylpivalate.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  0.88 (t, 3H), 1.18 (s, 9H), 1.22 (t, 3H), 1.65 (m, 2H), 2.5 (m, 2H), 2.9 (q, 2H), 5.41 (s, 2H), 5.81 (s, 2H), 6.75 (d, 2H), 7.04 (d, 2H), 7.2-7.35 (m, 2H), 7.44 (m, 1H), 7.9 (m, 1H).

Example 6Preparation of

5 Trimethylacetoxymethyl 4-ethyl-2-propyl-1-[[2'-(N-  
trimethylacetoxymethyl(tetrazol-5-yl))biphenyl-4-  
yl]methyl]imidazole-5-carboxylate

0.8 g of 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic acid was dissolved in 10 mL THF and 0.5 g chloromethyl pivalate and 2 mL triethylamine were added. The resulting solution was stirred overnight. The solvent was evaporated and the residue was flash chromatographed with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:9) to provide 0.257 g of the title compound.

15 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.87 (t, 3H), 1.18 (s, 18H), 1.22 (t, 3H), 1.71 (m, 2H), 2.62 (m, 2H), 2.87 (q, 2H), 5.51 (s, 2H), 5.88 (s, 2H), 6.39 (s, 2H), 6.89 (d, 2H), 7.1 (d, 2H), 7.2-7.35 (m, 3H), 7.82 (m, 1H).

Example 7Preparation of

20 Methoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(  
tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-  
carboxylate

25 Part A: Preparation of Chloromethyl methyl carbonate

1.22 mL MeOH was added slowly to a suspension of 1.29 g chloromethyl chloroformate and 1.52 g K<sub>2</sub>CO<sub>3</sub> in 50 mL CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred overnight at room temperature then suction filtered through glass fiber paper, washing with CH<sub>2</sub>Cl<sub>2</sub>. Evaporation of the filtrate provided 1.12 g of the product as an oil which was used without further purification.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>): 3.88 (s, 3H), 5.75 (s, 2H).

Part B: Preparation of Methoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate

5        0.44 g of the title product was obtained after chromatography (EtOAc) from 0.66 g 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid, 0.19 g chloromethyl methyl carbonate, 0.14 g K<sub>2</sub>CO<sub>3</sub>, and 0.25 g  
10 KI in 3 mL DMF from using the procedure described in Example 4 above.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.88 (t, 3H), 1.26 (t, 3H), 1.67 (m, 2H), 2.52 (t, 2H), 2.94 (q, 2H), 3.79 (s, 3H), 5.41 (s, 2H), 5.79 (s, 2H), 6.76 (m, 2H), 6.94 (m, 6H), 7.06  
15 (m, 2H), 7.2-7.5 (m, 12H), 7.9 (m, 1H).

Part C: Preparation of Methoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

20        0.21 g of the title compound was obtained after chromatography (0% to 10% MeOH/CHCl<sub>3</sub> gradient) from 0.35 g methoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate and 3 drops of 6 N HCl  
25 in 10 mL MeOH using the procedure described in Example 1 above.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.83 (2t, 6H), 1.55 (m, 2H), 2.18 (t, 2H), 2.45 (q, 2H), 3.75 (s, 3H), 5.4 (s, 2H), 5.78 (s, 2H), 6.75 (m, 2H), 7.03 (m, 2H), 7.43-7.65 (m, 3H),  
30 7.78 (m, 1H).

Example 8Preparation of

Methoxydimethylacetoxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

The title compound can be obtained using the procedure described in Example 4 above using chloromethyl methoxydimethylacetate.

Example 9Preparation of

t-Butoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

Part A: Preparation of t-Butyl chloromethyl carbonate

0.62 mL pyridine was added dropwise to a solution of 0.77 g chloromethyl chloroformate and 1.32 mL t-BuOH in 60 mL CH<sub>2</sub>Cl<sub>2</sub> cooled in an ice bath under an Ar atmosphere. The reaction was stirred 2 hours at 0°C then transferred to a separatory funnel. The reaction was washed twice with H<sub>2</sub>O, once with 10% CuSO<sub>4</sub>, once with brine and dried with MgSO<sub>4</sub>. Suction filtration and evaporation provided 0.55 g of desired product which was used without purification.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.48 (s, 9H), 5.65 (s, 2H).

Part B: Preparation of t-Butoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.22 mL Et<sub>3</sub>N was added to a mixture of 0.700 g 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate, 0.26 g t-butyl chloromethyl carbonate and 0.59 g n-Bu<sub>4</sub>NI in 5

mL dry THF under Ar. The reaction was stirred 6 days at room temperature and then concentrated on a rotary evaporator. The residue was partitioned between H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>, and the organic extracts dried with MgSO<sub>4</sub>. Flash chromatography using 1:1 EtOAc/petroleum ether (bp 40°-60 °C) gave 0.40 g of the title compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.88 (t, 3H), 1.05 (t, 3H), 1.68 (m, 2H), 2.5 (t, 3H), 2.93 (q, 2H), 5.43 (s, 2H), 5.75 (s, 2H), 6.78 (m, 2H), 6.93 (m, 6H), 7.08 (m, 2H), 7.2-7.53 (m, 2H), 7.90 (m, 1H).

Part C: Preparation of t-Butoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.43 g of the title compound was obtained after chromatography (0% to 10% MeOH/CHCl<sub>3</sub> gradient) from 0.40 g t-Butoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate and 3 drops 6 N HCl in 10 mL MeOH using the procedure described in Example 1 above.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.83 (m, 6H), 1.44 (s, 9H), 1.57 (m, 2H), 2.17 (m, 2H), 2.41 (m, 2H), 5.41 (s, 2H), 5.73 (s, 2H), 6.72 (m, 2H), 7.04 (m, 2H), 7.43 (m, 1H), 7.57 (m, 2H), 7.82 (m, 1H).

Example 10

Preparation of

1-Acetoxyethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

30

Part A: Preparation of 1-Chloroethyl acetate

0.25 g of zinc chloride was added to a mixture of 3.6 g of acetaldehyde dimethyl acetal and 3 g of acetyl

chloride. The mixture was warmed to 50°C for 4 hours then cooled. The reaction mixture was quenched with ice-cold NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated to give the crude acetate which was used without further purification.

MS (CH<sub>4</sub>-CI) m/z 123.0 (M+H)<sup>+</sup>.

Part B: Preparation of 1-Acetoxylethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

The title compound was obtained following the procedure described in Example 4 above using chloroethyl acetate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.91 (t, 3H), 1.21 (t, 3H), 1.71 (m, 2H), 1.75 (d, 3H), 2.05 (s, 3H), 2.6 (m, 2H), 2.75 (q, 2H), 5.41 (s, 2H), 6.85 (q, 1H), 6.92 (d, 2H), 7.08 (d, 2H), 7.2-7.35 (m, 3H), 7.8 (m, 1H).

Example 11

Preparation of

1-(Methoxycarbonyl)ethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

Part A: Preparation of 1-Chloroethyl chloroformate

108 g of ethyl chloroformate was dissolved in 190 mL of sulfuryl chloride and then 0.24 g benzoyl peroxide was added. The mixture was refluxed for 5 hours and then cooled slightly. Excess sulfuryl chloride was distilled, then the product mixture was distilled through a 1m spinning band column, 65°C at 22 torr, to give 96 g of the product.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.88 (d, 3H), 6.43 (q, 2H).

Part B: 1-Chloroethyl methyl carbonate

11.07 g of chloroethyl chloroformate, 5.8 g of methanol and 7.84 g of pyridine were added to 100 mL CH<sub>2</sub>Cl<sub>2</sub> at 0°C. The reaction was stirred for one hour then the reaction mixture was quenched with water and acidified with 1N HCl to pH 3. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated to give the crude carbonate (12 g) which was used without further purification.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.83 (d, 3H), 3.84 (s, 3H), 6.42 (q, 2H).

Part C: Preparation 1-(Methoxycarbonyl)ethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

The title compound was obtained following the procedure described in Example 4 above using chloroethyl methyl carbonate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.95 (m, 6H), 1.49 (d, 3H), 1.6 (m, 2H), 2.28 (m, 2H), 2.57 (q, 2H), 3.8 (s, 3H), 5.41 (dd, 2H), 6.77 (d, 2H), 6.82 (q, 1H), 7.05 (d, 2H), 7.42 (m, 1H), 7.57 (m, 2H), 7.84 (m, 1H).

Example 12

Preparation of

1-(t-Butoxycarbonyl)ethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

Part A: Preparation of 1-Chloroethyl t-butyl carbonate

12 g of chloroethyl chloroformate, 14.55 g of t-butanol and 8.5 g of pyridine were added to 100 mL CH<sub>2</sub>Cl<sub>2</sub> at 0°C. The reaction was stirred for one hour then the reaction mixture was quenched with water and

acidified with 1N HCl to pH 3. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated to give the crude carbonate (13.04 g) which was used without further purification.

5       <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.53 (s, 9H), 1.83 (d, 3H), 6.39 (q, 2H).

Part B: Preparation of 1-(t-Butoxycarbonyl)ethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

10       The title compound was obtained following the procedure outlined in Example 4 using chloroethyl t-butyl carbonate.

15       <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.92 (t, 3H), 1.14 (t, 3H), 1.14 (s, 9H), 1.51 (d, 3H), 1.62 (m, 2H), 2.47 (m, 2H), 2.92 (q, 2H), 5.4 (dd, 2H), 6.9 (d, 2H), 7.03 (d, 2H), 7.32 (m, 2H), 7.43 (m, 1H), 7.87 (m, 1H).

Example 13

Preparation of

20   1,3-Dioxo-5-methyl-cyclopenten-2-one-4-ylmethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

25   Part A: (1,3-Dioxo-5-methyl-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methylimidazole-5-carboxylate

30       A mixture of 0.659 g 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methylimidazole-5-carboxylic acid, 0.288 g 4-bromomethyl-1,3-dioxo-5-methyl-cyclopenten-2-one (Chem. Pharm. Bull. 32(6) 2241 (1984)), and 0.138 g K<sub>2</sub>CO<sub>3</sub> in 3 mL dimethylformamide was stirred at room temperature

under N<sub>2</sub> for 4 hours. The reaction was partitioned between 8 mL H<sub>2</sub>O and 40 mL ethyl acetate. The organic extract was washed with H<sub>2</sub>O (6 x 10 mL) and brine and dried with MgSO<sub>4</sub>. Filtration, evaporation, and flash  
5 chromatography of the residue with a 0% to 5% MeOH/CHCl<sub>3</sub> gradient provided 0.75 g of the title compound.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.88 (t, 3H, J=7.1 Hz), 1.14 (t, 3H, J=7.3 Hz), 1.67 (m, 2H), 2.06 (s, 3H), 2.52 (t, 2H, J=7.7 Hz), 2.91 (q, 2H, J=7.5 Hz), 4.81 (s, 2H), 5.55  
10 (s, 2H), 6.73 (m, 2H), 6.95 (m, 6H), 7.07 (m, 2H), 7.22-7.39 (m, 10H), 7.45 (m, 2H), 7.86 (m, 1H).

Part B: (1,3-Dioxo-5-methyl-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate  
15

4 drops 6 N HCl was added to a solution of 0.75 g of the above product in 10.5 mL MeOH in a N<sub>2</sub> atmosphere. The mixture was stirred at room temperature 2 days. The volatiles were evaporated and the residue immediately  
20 chromatographed using a 0% to 6% MeOH/CHCl<sub>3</sub> gradient. There was obtained 0.35 g of the desired compound as a white foam.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.80-0.93 (m, 6H), 1.50-1.62 (m, 2H), 2.05 (s, 3H), 2.18-2.20 (t, 2H), 2.40-2.55 (q, 2H),  
25 4.83 (s, 2H), 5.40 (s, 2H), 6.65-6.75 (d, 2H), 7.00-7.11 (d, 2H), 7.43-7.50 (m, 1H), 7.50-7.65 (m, 2H), 7.80-7.83 (m, 1H).

Example 14Preparation of

(5-(1,1-Dimethylethyl)-1,3-dioxo-cyclopenten-2-one-4-  
yl)methyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-  
5 yl)biphenyl-4-yl]methylimidazole-5-carboxylate

Part A: Preparation of 2,2-Dimethyl-4-hydroxy-3-  
pentanone

This compound was prepared from 2,2-dimethyl-3-  
10 pentanone (*J. Am. Chem. Soc.* **71**, 4141 (1949); *J. Am.*  
*Chem. Soc.* **81**, 2779 (1959)) by the general literature  
procedure (*Org. Synth.* **64**, 118 (1985)).

0.24 g of cuprous chloride was suspended in 100 mL  
diethyl ether and then 22.1 g of propionyl chloride was  
15 added. The reaction was heated to reflux and 88 mL of  
t-butyl magnesium chloride was added slowly to maintain  
reflux. The reaction was stirred overnight then poured  
into 200 g ice and the pH adjusted to 8 with solid  
NaHCO<sub>3</sub>. The reaction was extracted with ether, washed  
20 with 10% aq. NaHCO<sub>3</sub>, water and then brine followed by  
MgSO<sub>4</sub> drying. The product was purified by distillation  
to give 12.5 g of the ketone.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.15 (s, 9H), 1.27 (d, 3H), 3.40  
(br d, 1H), 4.56 (m, 1H).

25

Part B: 4-Bromomethyl-5-(1,1-dimethylethyl)-1,3-dioxo-  
cyclopenten-2-one

This material was prepared from 2,2-dimethyl-4-  
hydroxy-3-pentanone by the literature procedure  
30 described in (*Chem. Pharm. Bull.* **32**, 2241 (1984)).

1.94 g of 2,2-dimethyl-4-hydroxy-3-pentanone was  
dissolved in 15 mL of benzene and cooled to 0°C. 23 mL  
of phosgene in toluene was added followed by 23 mL  
pyridine and 20 mL toluene. The reaction was stirred

overnight, the solids filtered and the filtrate washed with 10% HCl then water and then dried with MgSO<sub>4</sub>.

Crude material was dissolved in 15 mL xylenes then 0.4 g p-TsOH was added and the reaction heated to reflux. The reaction was quenched with saturated aq. NaHCO<sub>3</sub> then distilled at 100-125°C at 1 torr.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.31 (s, 9H), 4.28 (s, 2H).

10 Part C: Preparation of (5-(1,1-Dimethylethyl)-1,3-dioxo-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenyl methyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.620 g of the title compound was obtained from 0.32 g 4-bromomethyl-5-(1,1-dimethylethyl)-1,3-dioxo-cyclopenten-2-one and 0.60 g 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid using the method shown in Example 13 above.

20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.86 (t, 3H), 1.23 (t, 3H), 1.25 (s, 9H), 1.70 (m, 2H), 2.49 (t, 2H), 2.90 (q, 2H), 4.99 (s, 2H), 5.40 (s, 2H), 6.75 (m, 1H), 6.95 (m, 6H), 7.08 (m, 2H), 7.2-7.5 (m, 12H), 7.88 (m, 1H).

25 Part D: Preparation of (5-(1,1-Dimethylethyl)-1,3-dioxo-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.40 g of the title compound was obtained from 0.62 g (5-(1,1-dimethylethyl)-1,3-dioxo-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate using the method shown in Example 13 above.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  0.85 (t, 3H), 0.93 (t, 3H), 1.26 (s, 9H), 1.60 (m, 2H), 2.25 (t, 2H), 2.56 (q, 2H), 5.01 (s, 2H), 5.41 (s, 2H), 6.77 (m, 2H), 7.08 (m, 2H), 7.42 (m, 1H), 7.59 (m, 2H), 7.88 (m, 1H).

5

#### Example 15

##### Preparation of

(1,3-dioxo-5-phenyl-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methylimidazole-5-carboxylate

10

##### Part A: Preparation of 2-Hydroxy-propiophenone

This was prepared from propiophenone by the general literature procedure described in *Org. Synth.* **64**, 118 (1985).

15

6 g of the TMS ether of propiophenone was dissolved in 225 mL hexane and cooled to  $-15^\circ\text{C}$ . 9.2 g MCPBA was added and the reaction stirred for 20 minutes at  $-15^\circ\text{C}$  then room temperature for 2 hours. The reaction was filtered then evaporated to give an oil which was diluted with 150 mL ethyl acetate, washed with 1.5N HCl and stirred for 20 minutes. This was neutralized with  $\text{NaHCO}_3$  then extracted with ethyl acetate then washed with brine. The product was purified by chromatography to give 2.52 g product.

20

25

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  1.46 (d, 3H), 3.83 (d, 1H) 5.17 (m, 1H), 7.51 (m, 2H), 7.63 (m, 1H), 7.92 (m, 2H).

##### Part B: 1,3-Dioxo-4-methyl-5-phenyl-cyclopenten-2-one

30

This compound was prepared from 2-hydroxy-propiophenone by the literature procedure described in *Liebigs Ann. Chem.* **764**, 116 (1972).

The hydroxyketone was dissolved in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  and 26 mL phosgene in toluene was added followed by 3 g

dimethylaniline. Stirred overnight at room temperature. Washed with 10% HCl, water and brine then dried with MgSO<sub>4</sub>. Distillation (100°C at 0.06 torr) gave 2.74 g of product.

5       <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 2.39 (s, 3H), 7.35-7.50 (m, 5H).

Part C: 4-Bromomethyl-1,3-dioxo-5-phenyl-cyclopenten-2-one

This compound was prepared from 1,3-dioxo-4-methyl-5-phenyl-cyclopenten-2-one by the literature procedure described in *Chem. Pharm. Bull.* **32**, 2241 (1984).

2.74 g of 1,3-dioxo-4-methyl-5-phenyl-cyclopenten-2-one, 3.32 g NBS and 0.0613 g AIBN were refluxed overnight. The reaction was cooled to 0°C then filtered. The filtrate was evaporated then recrystallized from benzene/cyclohexane to give 1.5 g of product.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 4.45 (s, 2H), 7.55 (m, 5H).

20 Part D: (1,3-Dioxo-5-phenyl-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.220 g of the title compound were obtained from 0.3826 g 4-bromomethyl-1,3-dioxo-5-phenyl-cyclopenten-2-one and 0.6588 g 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylic acid using the procedure described in Example 1 above.

Part E: Preparation of (1,3-Dioxo-5-phenyl-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate

0.15 g of the title compound was obtained from 0.22  
5 g (1,3-dioxo-5-phenyl-cyclopenten-2-one-4-yl)methyl 4-ethyl-2-propyl-1-[[2'-(N-triphenylmethyl(tetrazol-5-yl))biphenyl-4-yl]methyl]imidazole-5-carboxylate using the procedure described in Example 1 above.

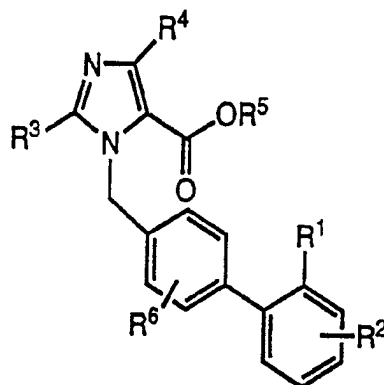
R<sub>f</sub> (silica gel, MeOH/CHCl<sub>3</sub> 1:9) 0.45.

10

The compounds described in Examples 1-15 above are set forth in Table 1.



Table 2



Example	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>
16	Tet	H	Et	Et	CH <sub>2</sub> O <sub>2</sub> CC(CH <sub>3</sub> ) <sub>3</sub>	H
17	Tet	H	n-Pr	Et	CH <sub>2</sub> O <sub>2</sub> CC(CH <sub>3</sub> ) <sub>3</sub>	H
18	Tet	H	n-Bu	Et	CH <sub>2</sub> O <sub>2</sub> CC(CH <sub>3</sub> ) <sub>3</sub>	H
19	Tet	H	n-Pr	Et	CH <sub>2</sub> O <sub>2</sub> CC(CH <sub>3</sub> ) <sub>3</sub>	F
20	Tet	H	n-Pr	C <sub>2</sub> F <sub>5</sub>	CH <sub>2</sub> O <sub>2</sub> CC(CH <sub>3</sub> ) <sub>3</sub>	F
21	Tet	Et	n-Pr	Cl	CH <sub>2</sub> O <sub>2</sub> COC(CH <sub>3</sub> ) <sub>3</sub>	H
22	Tet	n-Pr	n-Bu	Cl	CH <sub>2</sub> O <sub>2</sub> COC(CH <sub>3</sub> ) <sub>3</sub>	H
23	Tet	OEt	n-Pr	Cl	CH <sub>2</sub> O <sub>2</sub> COC(OCH <sub>3</sub> )(CH <sub>3</sub> ) <sub>2</sub>	H
24	Tet	H	n-Bu	n-Pr	CH <sub>2</sub> O <sub>2</sub> COCH(CH <sub>3</sub> ) <sub>2</sub>	Me
25	Tet	H	n-Bu	n-Pr	CH <sub>2</sub> O <sub>2</sub> COCH(CH <sub>3</sub> ) <sub>2</sub>	Me

Tet = Tetrazole

Utility

Angiotensin-II (AII) produces numerous biological responses (e.g. vasoconstriction) through stimulation of its receptors on cell membranes. For the purpose of  
5 identifying compounds such as AII antagonists which are capable of interacting with the AII receptor, a ligand-receptor binding assay was utilized for the initial screen. The assay was carried out according to the method described by [Chiu, et al., Receptor, 1 33,  
10 (1990)]. In brief, aliquots of a freshly prepared particulate fraction of rat adrenal cortex were incubated with 0.05 nM [<sup>125</sup>I] AII and varying concentrations of potential AII antagonists in a Tris buffer. After a 1 h incubation the reaction was  
15 terminated by addition of cold assay buffer. The bound and free radioactivity were rapidly separated through glass-fiber filters, and the trapped radioactivity was quantitated by scintillation counting. The inhibitory concentration (IC<sub>50</sub>) of potential AII antagonists which  
20 gives 50% displacement of the total specifically bound [<sup>125</sup>I] AII is presented as a measure of the affinity of such compound for the AII receptor.

Using the assay method described above, the compounds of this invention are found to exhibit an  
25 activity of at least IC<sub>50</sub> <10 micromolar, thereby demonstrating and confirming the activity of these compounds as effective AII antagonists. Results are presented in Table 3.

Table 3

Angiotensin II	
Example	Receptor Binding
	IC <sub>50</sub> nM
2	100
5	2
6	20
7	3
9	6
10	20
11	4
12	5
13	3
14	3
15	6

The potential antihypertensive effects of the compounds of this invention may be demonstrated by administering the compounds to awake rats made  
5 hypertensive by ligation of the left renal artery [Cangiano, et al., *J. Pharmacol. Exp. Ther.*, 1979, 208, 310]. This procedure increases blood pressure by increasing renin production with consequent elevation of AII levels. Compounds are administered intravenously  
10 via cannula in the jugular vein to give a cumulative dose of 10 mg/kg. Arterial blood pressure is continuously measured directly through a carotid artery cannula and recorded using a pressure transducer and a polygraph. Blood pressure levels after treatment are  
15 compared to pretreatment levels to determine the antihypertensive effects of the compounds.

Using the in vivo methodology described above, the compounds of this invention are found to exhibit an activity (intravenous) which is 10 mg/kg or less,

and/or an activity (oral) which is 100 mg/kg or less, thereby demonstrating and confirming the utility of these compounds as effective agents in lowering blood pressure. The results are described in Table 4.

Table 4

<u>Examples</u>	Oral Antihypertensive Effects in Renal Hypertensive Rats	
	<u>ED<sub>30</sub> mg/kg</u>	
5		0.03
8		0.03
9		0.02
11		0.02
12		0.3
13		0.1
14		0.3
15		0.3

The compounds of the invention can be administered for the treatment of hypertension by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration can be parenteral, i.e., subcutaneous, intravenous, intramuscular, or intraperitoneal. Preferably, administration is by the oral route.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the

chosen route of administration and standard pharmaceutical practice.

The compounds of the invention are useful in treating hypertension. They are also of value in the management of acute and chronic congestive heart failure and angina. These compounds may also be expected to be useful in the treatment of primary and secondary hyperaldosteronism; renal diseases such as diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage renal disease, used in renal transplant therapy, and to treat renovascular hypertension, scleroderma, left ventricular dysfunction, systolic and diastolic dysfunction, diabetic retinopathy and in the management of vascular disorders such as migrane, Raynaud's disease, and as prophylaxis to minimize the atherosclerotic process and neointimal hyperplasia following angioplasty or vascular injury and to retard the onset of type II diabetes. The application of the compounds of this invention for these and similar disorders will be apparent to those skilled in the art.

The compounds of this invention are also useful to treat elevated intraocular pressure and to enhance retinal blood flow and can be administered to patients in need of such treatment with typical pharmaceutical formulations such as tablets, capsules, injectables and the like as well as topical ocular formulations in the form of solutions, ointments, inserts, gels and the like. Pharmaceutical formulations prepared to treat intraocular pressure would typically containing about 0.1% to 15% by weight, preferably 0.5% to 2% by weight, of a compound of this invention. For this use, the compounds of this invention may also be used in combination with other medications for the treatment of

glaucoma including choline esterase inhibitors such as physostigmine salicylate or demecarium bromide, parasympathomimetic agents such as pilocarpine nitrate,  $\beta$ -adrenergic antagonists such as timolol maleate, 5 adrenergic agonists such as epinephrine and carbonic anhydrase inhibitors such as MK-507.

The term, "a warm-blooded animal" as used herein means a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

10 In the management of hypertension and the clinical conditions noted above, the compounds of this invention may be utilized with a pharmaceutical carrier in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal 15 administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered a warm-blood animal in need of such treatment in dosages that will provide optimal 20 pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets being followed by a patient, concurrent medication, and other factors which those skilled in the art will 25 recognize, the dosage range will generally be about 1 to 1000 mg per patient per day which can be administered in single or multiple doses. Preferably, the dosage range will be about 5 to 500 mg per patient per day; more preferably about 5 to 300 mg per patient per day.

30 The compounds of this invention can also be administered in combination with other antihypertensives and/or diuretics. For example, the compounds of this invention can be given in combination with diuretics such as hydrochlorothiazide, chlorothiazide,

chlorthalidone, methyclothiazide, furosemide, ethacrynic acid, triamterene, amiloride spironolactone and atriopeptin; calcium channel blockers, such as diltiazem, felodipine, nifedipine, amlodipine, 5 nimodipine, isradipine, nitrendipine and verapamil;  $\beta$ -adrenergic antagonists such as timolol, atenolol, metoprolol, propanolol, nadolol and pindolol; angiotensin converting enzyme inhibitors such as enalapril, lisinopril, captopril, ramipril, quinapril 10 and zofenopril; renin inhibitors such as A-69729, FK 906 and FK 744;  $\alpha$ -adrenergic antagonists such as prazosin, doxazosin, and terazosin; sympatholytic agents such as methyl dopa, clonidine and guanabenz; atriopeptidase inhibitors (alone or with ANP) such as UK-79300; 15 serotonin antagonists such as ketanserin;  $A_2$ -adrenosine receptor agonists such as CGS 22492C; potassium channel agonists such as pinacidil and cromakalim; and various other antihypertensive drugs including reserpine, minoxidil, guanethidine, hydralazine hydrochloride and 20 sodium nitroprusside as well as combinations of the above-named drugs. Combinations useful in the management of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such dobutamine and xamoterol and 25 phosphodiesterase inhibitors including amrinone and milrinone.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum 30 recommended levels for the entities when they are given singly. To illustrate these combinations, one of the angiotensin-II antagonists of this invention effective clinically in the 5-500 milligrams per day range can be effectively combined at levels at the 1.0-500 milligrams

per day range with the following compounds at the indicated per day dose range; hydrochlorothiazide (6-100 mg), chlorothiazide (1250-500 mg), furosemide (5-80 mg), propranolol (10-480 mg), timolol maleate (1-20 mg),  
5 methyldopa (125-2000 mg), felodipine (1-20 mg), nifedipine (5-120 mg), nitrendipine (5-60 mg), and diltiazem (30-540 mg). In addition, triple drug combinations of hydrochlorothiazide (5-100 mg) plus  
10 amiloride (5-20 mg) plus angiotensin-II antagonists of this invention (1-500 mg) or hydrochlorothiazide (5-100 mg) plus timolol maleate (5-60 mg) plus an angiotensin-II antagonists of this invention (1-500 mg) or  
hydrochlorothiazide (5-200 mg) and nifedipine (5-60 mg) plus an angiotensin-II antagonists of this invention (1-  
15 500 mg) are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of  
20 the disease, weight of patient, special diets and other factors.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs,  
25 syrups, and suspension. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed  
30 tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated for film coated

to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can  
5 contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols  
10 are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and, if necessary, buffer substances. Antioxidizing agents such as sodium  
15 bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or  
20 propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol., a standard reference text in this field.

Useful pharmaceutical dosage-forms for  
25 administration of the compounds of this invention can be illustrated as follows:

#### Capsules

A large number of unit capsules are prepared by  
30 filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

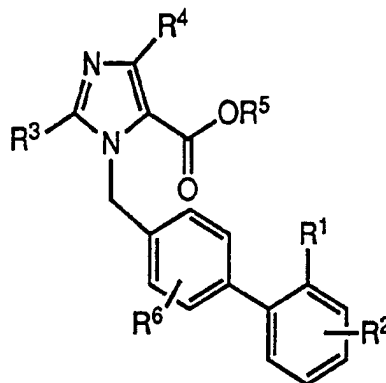
A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

WHAT IS CLAIMED IS:

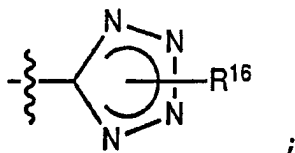
1. A compound of the formula:



I

5 wherein

R<sup>1</sup> is -CO<sub>2</sub>H or



R<sup>2</sup> is

- (a) H,  
 10 (b) C1-C5-alkyl,  
 (c) C1-C5-alkoxy,  
 (d) halo (F, Cl),  
 (e) phenyl;

15 R<sup>3</sup> is C1-C5-alkyl, C2-C5-alkenyl, C2-C5-alkynyl;

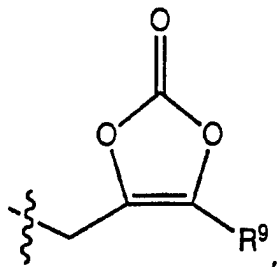
R<sup>4</sup> is

- (a) H,  
 (b) halo (Cl, Br, I),  
 (c) C1-C6-alkyl,  
 20 (d) C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1);

R<sup>5</sup> is

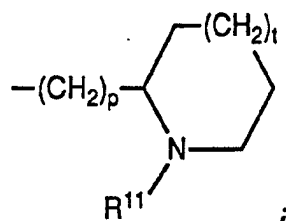
- (a) C1-C5-alkyl,  
 (b) C2-C5-alkenyl,  
 (c) C2-C5-alkynyl,

- (d)  $-(CH_2)_p NR^{12} R^{13}$ ,  
 (e)  $-(CH_2)_s CH(R^7) (CH_2)_{s'} O_2 CR^8$ ,  
 (f)



- 5 (g)  $-(CH_2)_p CO_2 R^{10}$ ,

(h)



$R^6$  is

- 10 (a) H,  
 (b) halogen (F, Cl, Br, I),  
 (c) C1-C5-alkyl,  
 (d) -OH,  
 (e) C1-C4-alkoxy,  
 15 (f) -NO<sub>2</sub>,  
 (g) -NR<sup>12</sup>R<sup>13</sup>,  
 (h) -NR<sup>12</sup>COR<sup>15</sup>,  
 (i) -NR<sup>12</sup>CO<sub>2</sub>R<sup>15</sup>,  
 (j) -S(O)<sub>r</sub>R<sup>14</sup> where r is 0, 1 or 2,  
 20 (h) -CO<sub>2</sub>R<sup>15</sup>,  
 (i) -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),  
 (J) -OC<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1), or  
 (K) -CN;

$R^7$  is H or C1-C4-alkyl;

25  $R^8$  is

- (a) H,
- (b) C1-C5-alkoxy,
- (c) C1-C5-alkyl optionally substituted with a group consisting of:

- 5           i) C1-C5-alkoxy,
- ii) aryl, wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I),
- 10           C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C5-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1);

R<sup>9</sup> is

- 15           (a) C1-C5-alkyl,
- (b) -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),
- (c) C1-C5-alkyl optionally substituted with a group consisting of:
  - 20           i) C1-C5-alkoxy,
  - ii) phenyl or phenyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where
  - 25           v=1 to 3 and w=1 to (2v+1),
  - iii) benzyl or benzyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where
  - 30           v=1 to 3 and w=1 to (2v+1);

R<sup>10</sup> is

- (a) phenyl or phenyl substituted with at least one substituent selected from the group

consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1),

- 5 (b) benzyl or benzyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, -NO<sub>2</sub>, -S(O)<sub>r</sub>(C1-C4-alkyl), -OH, -NR<sup>12</sup>R<sup>13</sup>, -CO<sub>2</sub>R<sup>15</sup>, and -C<sub>v</sub>F<sub>w</sub> where v=1 to 3 and w=1 to (2v+1);

R<sup>11</sup> is H, C1-C5-alkyl or benzyl;

R<sup>12</sup> and R<sup>13</sup> are independently H, C1-C5-alkyl, phenyl or benzyl;

R<sup>14</sup> is CF<sub>3</sub>, C1-C5-alkyl, or phenyl;

- 15 R<sup>15</sup> is H, C1-C5-alkyl, or NR<sup>12</sup>R<sup>13</sup>;

R<sup>16</sup> is H or CH<sub>2</sub>O<sub>2</sub>CC(CH<sub>3</sub>)<sub>3</sub>;

p is 1-5;

r is 0-2;

s and s' are 0-5;

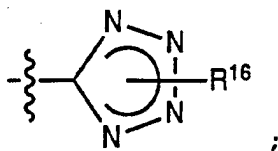
- 20 t is 0 or 1;

or a pharmaceutically acceptable salt thereof provided that when R<sup>4</sup> is H, halo (Cl, Br, I) or CF<sub>3</sub> then R<sup>5</sup> cannot be CH(CH<sub>3</sub>)O<sub>2</sub>CR<sup>8</sup> wherein R<sup>8</sup> is C1-C5 alkoxy.

25

2. A compound according to claim 1 wherein

R<sup>1</sup> is



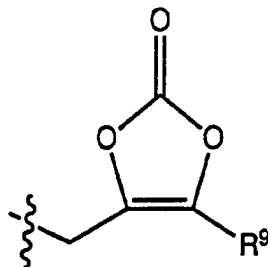
R<sup>2</sup> is H;

- 30 R<sup>3</sup> is C1-C5-alkyl;

R<sup>5</sup> is

(a) -(CH<sub>2</sub>)<sub>s</sub>CH(R<sup>7</sup>)(CH<sub>2</sub>)<sub>s'</sub>O<sub>2</sub>CR<sup>8</sup>

(b)



R<sup>6</sup> is H;

R<sup>7</sup> is H;

5 R<sup>8</sup> is

(a) H,

(b) C1-C5-alkoxy,

(c) C1-C5-alkyl optionally substituted with a group consisting of:

10 i) C1-C5-alkoxy;

R<sup>9</sup> is

(a) C1-C5-alkyl,

(b) C1-C5-alkyl optionally substituted with a group consisting of:

15 i) C1-C5-alkoxy,

ii) phenyl or phenyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), alkyl, C1-C5-alkoxy, -OH;

20 iii) benzyl or benzyl substituted with at least one substituent selected from the group consisting of halo (F, Cl, Br, I), C1-C5-alkoxy, -OH;

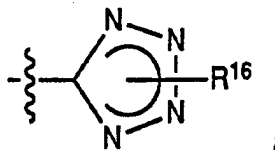
p is 1;

25 s is 1;

s' is 0.

3. A compound according to claim 1 wherein

R<sup>1</sup> is



R<sup>2</sup> is H;

R<sup>3</sup> is C1-C5-alkyl;

5 R<sup>5</sup> is  $-(CH_2)_sCH(R^7)(CH_2)_{s'}O_2CR^8$ ;

R<sup>7</sup> is H;

R<sup>8</sup> is

(a) C1-C5-alkoxy,

(b) C1-C5-alkyl optionally substituted with a

10 group consisting of:

i) C1-C5-alkoxy;

p is 1;

s is 1;

s' is 0.

15

4. A compound according to claim 1 which is trimethylacetoxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate.

20

5. A compound according to claim 1 which is methoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate.

25

6. A compound according to claim 1 which is t-butoxycarbonyloxymethyl 4-ethyl-2-propyl-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylate.

30

7. A compound according to claim 1 which is  
1-(Methoxycarbonyl)ethyl 4-ethyl-2-propyl-1-[[2'-  
(tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-  
carboxylate.

5

8. A pharmaceutical composition comprising a  
pharmaceutically suitable carrier and a therapeutically  
effective amount of the compound of any one of claims 1  
through 7.

10

9. A method of treating hypertension in a warm-  
blooded animal comprising orally administering to the  
animal a therapeutically effective amount of a compound  
of any one of claims 1 through 7.

15

10. A method of treating congestive heart failure  
in a warm-blooded animal comprising orally administering  
to the animal a therapeutically effective amount of a  
compound of any one of claims 1 through 7.

20

## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 93/07103

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D233/90 C07D403/10 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 324 377 (E. I. DU PONT DE NEMOURS AND COMPANY) 19 July 1989 cited in the application see claims 1,10; examples 126,140h,140i,314a,347 ----	1,8
X	WO,A,92 00977 (E. I. DU PONT DE NEMOURS AND COMPANY) 23 January 1992 cited in the application see page 10, line 4 - line 12 -----	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

3 November 1993

Date of mailing of the international search report

25. 11. 93

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

VOYIAZOGLU, D

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/07103

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0324377	19-07-89	AU-A- 2777189	13-07-89
		JP-T- 3501020	07-03-91
		WO-A- 8906233	13-07-89
		US-A- 5138069	11-08-92
		US-A- 5128355	07-07-92
		US-A- 5153197	06-10-92
		US-A- 5155118	13-10-92
		US-A- 5210079	11-05-93
-----			
WO-A-9200977	23-01-92	US-A- 5137902	11-08-92
		AU-B- 639400	22-07-93
		AU-A- 8311691	04-02-92
		EP-A- 0539509	05-05-93
-----			